Prepared from FORM PTO-1390

Transmittal Letter to the United States Designated/Elected Office (DO/EO/US)

JC09 Rec'd PCT/PTO 14 JUN 2001

Customer No.	026418	
Attorney's Docket No.:	JG-HK-5084 / 500572.20040	
U.S. Application No.:	09/868106	
International Application No.:	PCT/JP98/05810	
International Filing Date:	DECEMBER 22, 1998	22 DECEMBER 1998
Priority Date Claimed:	DECEMBER 22, 1998	22 DECEMBER 1998
Title of Invention:	PREVENTIVE AGAINST RESPIRATORY INFECTIOUS DISEASES	
Applicant(s) for (DO/EO/US):	Tsuyoshi NAGATAKE	

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

[X] 1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
[ ] 2. This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
[ ] 3. This express request to begin national examination procedures [35 U.S.C. 371 (f)] at any time rather than delay examination until the expiration of the applicable time limit set forth in 35 U.S.C. 371(b) and PCT Articles 22 and
[ ] 4. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
[X] 5. A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a) x is transmitted herewith (required only if not transmitted by the International Bureau)
   b) __ has been transmitted by the international Bureau
   c) __ is not required, as the application was filed in the United States Receiving Office (RO/US)
[X] 6. A translation of the International Application into English [35 U.S.C. 371(c)(2)]
[ ] 7. Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a) __ are transmitted herewith (required only if not transmitted by the International Bureau)
   b) __ have been transmitted by the International Bureau
   c) __ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d) __ have not been made and will not be made
[ ] 8. A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]
[X] 9. An EXECUTED Oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)]
[ ] 10. A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)]

Items 11. to 16. Below concern other document(s) or information included:

[ ] 11. An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98
[X] 12. An Assignment document for recording. A separate cover sheet (PTO-1619A) in compliance with 37 CFR 3.28 and 3.31 is included.
[X] 13. x A **FIRST** preliminary amendment
   __ A **SECOND** or **SUBSEQUENT** preliminary amendment
[ ] 14. A **substitute specification**
[ ] 15. A change of power of attorney and/or address letter
[X] 16. (other items or information) **PCT/RO/101, PCT/IB/308 dated 29JUN00, Publication No. WO 00/37070 dated 29JUN00 w/JP Search Report 16MAR99 and PCT/IPEA/409 dated 27FEB01.**

EXPRESS MAIL No.: **EL 915 668 498 US** Deposited: **June 14, 2001**
I hereby certify that this correspondence is being deposited with the United States Postal Service Express mail under 37 CFR 1.10 on the date indicated above and is addressed to: BOX PCT, Commissioner for Patents, Washington, DC 20231.

/Ruth Montalvo/ Date: **June 14, 2001**

JC03 Rec'd PCT/PTO 14 JUN 2001

U.S. Application No. (if known, see 37 C.F.R. 1.50):
International Application No.: **PCT/JP98/05810**
Attorney's Docket No: JG-HK-5084 / **500572.20040**

09/868106

	CALCULATIONS	PTO USE ONLY
[X] 17. The following fees are submitted:		
BASIC NATIONAL FEE [37 CFR 1.492(a)(1)-(5)]		
[X] Search Report has been prepared by the EPO or JPO..... $ 860.00		
[ ] International preliminary examination fee paid to USPTO [37 CFR 1.482]..... $ 690.00		
[ ] No International preliminary examination fee paid to USPTO [37 CFR 1.482] but International search fee paid to USPTO [37 CFR 1.445(a)(2)..... $ 710.00		
[ ] Neither International preliminary examination fee [37 CFR 1.482] nor International search fee [37 CFR 1.445(a)(2)] paid to USPTO..... $ 1,000.00		
[ ] International preliminary examination fee paid to USPTO [37 CFR 1.482] and all claims satisfied provisions of PCT Article 33(1)-(4)..... $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT:	**$860.00**	

Claims	Number Filed		Number Extra	Rate		
Total Claims	**1**	-20		x $ 18. =		
Indep. Claims	**1**	-03		x $ 80. =		
[___] Multiple Dependent Claim(s) (if applicable)				+ $ 270. =		
				TOTAL OF ABOVE CALCULATIONS:	**$860.00**	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date [37 CFR 1.492(e)]						
				TOTAL OF ABOVE CALCULATIONS:	**$860.00**	
Applicant claims Small Entity Status [See 37 CFR 1.27] Reduction by ½ for filing by small entity						
				SUBTOTAL:	**$860.00**	
Processing fee of $130.00 for furnishing the English Translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date [37 CFR 1.492(f)]						
				TOTAL NATIONAL FEE:	**$860.00**	
Fee for recording the enclosed assignment [37 CFR 1.21(h)] The assignment must be accompanied by an appropriate cover sheet (PTO-1595) [37 CFR 3.28, 3.31].$ 40.00 per property +					**$ 40.00**	
				TOTAL FEE(S):	**$900.00**	
				AMOUNTS TO BE REFUNDED OR CHARGED	**REFUNDED** **CHARGED**	$ $

[X] Check in the amount of **$ 900.00** to cover the above fees is enclosed. (The Commissioner is hereby authorized to charge any additional fees required with this submission or to credit any overpayment to Deposit Account No: 50-1529.)

NOTE: Where an appropriate time limit under 36 CFR 1.494 or 1.495 has not been met, a petition to revive [37 CFR 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Jules E. Goldberg, Esq. **(Customer No. 026418)**
Reed Smith LLP
375 Park Avenue
New York, NY 10152

Jules E. Goldberg
Name (Tel. (212) 521-5400)

Signature

24,408
Reg. No.

June 14, 2001
Date

EXPRESS MAIL No.: **EL 915 668 498 US** Deposited: **June 14, 2001**
I hereby certify that this correspondence is being deposited with the United States Postal Service Express mail under 37 CFR 1.10 on the date indicated above and is addressed to: Box PCT, Commissioner for Patents, Washington, DC 20231

By: Ruth Montalvo / **Ruth Montalvo** Date: **06/14/01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BOX PCT
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

The above-identified application is filed concurrently herewith, please amend the specification as follows:

Page 2, before BACKGROUND OF THE INVENTION insert the following:

--CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims priority of Japanese International Application No. PCT/JP98/05810 filed December 22, 1998, the complete disclosure of which is hereby incorporated by reference. --

REMARKS

The above amendment is submitted to include the cross-referencing of the Japanese priority. No new matter is added. Entry into the application is earnestly solicited.

Respectfully submitted,

JEG:ram
June 14, 2001
Tel. (212) 521-5400

Jules E. Goldberg - Reg. No. 24,408
Reed Smith LLP
375 Park Avenue
New York, NY 10152

09/868106

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PREVENTIVE AGAINST RESPIRATORY INFECTIOUS DISEASES

Background of the Invention:

Field of the Invention:

The present invention relates to a preventive against a respiratory infectious disease which prevents adhesion of contagium onto the upper respiratory tract.

Description of the Related Art:

For treatment of a respiratory infectious disease, after-treatments against the infection have been widely investigated, such as bactericidal disinfection by an antimicrobial, anti-inflammation treatment by anti-inflammatory agent, promotion of excretion of sputum by an expectorant, and so forth. However, for prevention of the infection, only virus adhesion-inhibiting agents are being developed although the prevention of infection is recognized to be important. The prevention of adhesion of the bacterial cells onto the respiratory tract has not been reported at all. No effective medicine is known for this purpose.

The adhesion ability of Moraxella (Branhamela) catarrhalis, which is known as one of the five kinds of main inflammation-causing bacteria, onto pharynx epithelium (mucous membrane of upper respiratory tract) is reported to correlate significantly with development of the infection in the lower respiratory tract (Mubaki N. et al.: Tohuku J. Exp. Med. 153, 111-121, 1987).

From this, it is expected that prevention of the adhesion of the respiratory contagium onto the upper respiratory tract could be the first step of preventing the

lower respiratory tract infection. Actually, mouth-washing with a disinfectant has been proved clinically to be effective for the prevention of the infection. However, no medicine has been reported which prevents directly the adhesion of the respiratory contagium onto the upper respiratory tract.

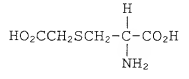
The wide use of the antimicrobials against the respiratory infectious disease has produced various new problems such as increase of tolerable bacteria due to the fact that infants and elders often suffer from repeated infection by virus, bacteria, etc. Patients with chronic respiratory infectious disease or with immune depression against various disease germs are facing the danger of the repeated infection with the bacteria. The establishment of an effective infection prevention method for such patients is the problem to be solved. Therefore, it is desirable for such easily infectious patients to prevent the disease before the human body is infected by a respiratory contagium.

Disclosure of the Invention:

The inventors of the present invention noticed that the first step of the respiratory infectious disease is adhesion of the contagium onto an upper respiratory tract, and expected that the development of the respiratory disease could be prevented by inhibiting adherence of the contagium onto the respiratory tract. Therefore, the inventors of the present invention tested carbocysteine, a well-known

expectorant, for the effect of prevention of adhesion of a bacteria onto the respiratory tract, and found the remarkable effect thereof.

The present invention relates to a preventive against a respiratory infectious disease, the preventive containing, as the active ingredient, carbocysteine represented by the chemical formula (1) below:



(1)

The carbocysteine is a cysteine derivative represented by the chemical formula (1), being useful as an expectorant. The carbocysteine was developed by Laboratories Joulie Co. in France, and was commercialized in 1965 with the trade name "Rhinathiol". Later in United Kingdom, carbocysteine was commercialized by Berk Pharmaceuticals Co. with a trade name "Mucodyne" in 1972. At present, carbocysteine is commercialized in 14 countries in the world.

In Japan, carbocysteine was developed by Kyorin Pharmaceutical Co., Ltd., approved for production by Ministry of Health and Welfare (Japan) in 1981, and commercialized with trade name "Mucodyne", and is being used widely as a safe expectorant.

Carbocysteine is known to have various effects: promotion of excretion of sputum by improving its properties (Brown D.T: Drug Intelligence Clin. Pharmacol., 22. 603-608, 1988), promotion of repair of the cilium and improvement of

its transporting ability (Ogihara M. et al.: Kikanshigaku (Treatise on Bronchia), 1982), and so forth. However, its effect of inhibiting adhesion of bacteria has not been known.

Carbocysteine as a respiratory infectious disease preventive can be administered to a human body in a pharmaceutically known formulation form through a known administration route. For example, carbocysteine can be administered orally in a form of such as powders, tablets, capsules, grains, granules, and syrups. The amount of administration of carbocysteine as the preventive against the respiratory infectious disease ranges preferably from 250 to 2000 mg, more preferably from 250 to 1000 mg per dose, and preferably three doses per day, depending on the age, the body weight, and the symptom of the patient.

Brief Description of the Drawings:

Fig. 1 is a graph showing the test results of Example 1.

Fig. 2 is a graph showing the test results of Example 2.

Examples:

[Example 1]

The effect of the carbocysteine for inhibiting the adhesion of Moraxella (Branhamela) catarrhalis, a respiratory contagium, onto a human pharynx epithelium cells was evaluated by vitro experiments.

(1) Pharynx epithelium cells:

With full informed consent, cell samples were collected by rubbing, with swabs, portions of pharynx of two healthy persons of 28-54 years of age and of 19 patients of 53-75 years of age having respiratory infectious disease.

(2) Moraxella (Branhamela) catarrhalis:

The bacterial cells were isolated from the expectoration, and the isolated cells were cultured, by using clinically separated strains having clear inflammation tendency.

(3) Adhesion test:

A liquid suspension of Moraxella (Branhamela) catarrhalis was mixed with a liquid suspension of the pharynx epithelium cells. A solution of carbocysteine was added thereto to attain the final concentrations ranging from 1 to 100 μg/mL. After left standing for a prescribed time, the Moraxella (Branhamela) catarrhalis not adhering to the pharynx epithelium cells were removed by centrifugation. The remaining pharynx epithelium cells were fixed with a cyto-spin onto a slide glass, and were stained by Gram's method. The number of Moraxella (Branhamela) catarrhalis adhering on the pharynx epithelium was counted with an optical microscope. A control was employed which did not contain carbocysteine.

(4) Evaluation:

In the microscopical examination, fifty cells of the pharynx epithelium were randomly selected. The average number of Moraxella (Branhamela) catarrhalis adhering on one pharynx epithelium cell randomly selected was counted. The

adhesion ratio was calculated in comparison with the control taken as 100%.

(5) Results:

Carbocysteine inhibited the adhesion of Moraxella (Branhamela) catarrhalis to the pharynx epithelium cells of the healthy persons and patients as shown in Fig. 1.

[Example 2]

The effect of the carbocysteine for inhibiting the adhesion of Moraxella (Branhamela) catarrhalis onto a human pharynx epithelium cells was evaluated by oral administration.

(1) Objects:

Five healthy persons of 30-54 years of age, and four patients of 50-75 years of age having chronic obstructive pulmonary disease were selected as the objects with full informed consent.

(2) Administration method:

Carbocysteine was administered orally at a dose of 500 mg, three times a day for 7 days.

(3) Adhesion test:

The pharynx epithelium cells were collected in the same manner as in Example 1 before the carbocysteine administration; 2 hours after the first administration; 3 days and 7 days after the start of the administration; and 7 days after completion of the administration. The respective liquid suspensions of the pharynx epithelium cells were mixed with a liquid suspension of Moraxella (Branhamela) catarrhalis. After a prescribed time, the Moraxella

(Branhamela) catarrhalis not adhering to the pharynx epithelium cells were washed and removed by centrifugation. The remaining pharynx epithelium cells were fixed with a cyto-spin onto a slide glass, and were stained by Gram's method. The number of strains of Moraxella (Branhamela) catarrhalis adhering on the pharynx epithelium cells was counted with an optical microscope. The pharynx epithelium cells collected before the carbocysteine administration were used as the control.

(4) Evaluation:

In the microscopical examination, fifty cells were randomly selected. The average number of Moraxella (Branhamela) catarrhalis adhering per one of the fifty pharynx epithelium cells randomly selected was counted. The adhesion ratio was calculated in comparison with the control taken as 100%.

(5) Results:

The adhesion ratio was lowered by administration of carbocysteine. The adhesion ratio decreases during the continued administration with lapse of time, and became lowest by 7 days of the administration. After completion of the administration, the ratio increased to the level near 100 % in 7 days. Table 2 shows the results.

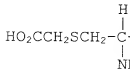
Industrial Applicability:

The inventors of the present invention have found that carbocysteine inhibits effectively the adhesion of respiratory contagium onto pharynx epithelium cells in vitro

as well as in vivo (oral administration). Therefore, carbocysteine can be a preventive against the respiratory infectious disease, being effective in the initial-infective step, namely effective to suppress adhesion of the bacteria onto an upper respiratory tract. The carbocysteine is promising in decrease of acute exacerbation frequency, and prevention of bacterial infection of humans having depressed immunity, and retardation of the increase of tolerant bacteria caused by wide use of the antimicrobials.

What is claimed is:

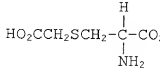
1. A preventive against respiratory infectious disease, containing as an active ingredient represented by Chemical Formula (1):



(1)

Abstract of the Disclosure:

A preventive against respiratory infectious disease is disclosed which contains carbocysteine represented by Chemical Formula (1) as the active ingredient:



(1)

This preventive of the present invention can be a preventive against the respiratory infectious disease, effective in the initial-infective stage, namely effective to suppress adhesion of the bacteria onto an upper respiratory tract. The carbocysteine is promising in decrease of acute exacerbation frequency, and prevention of bacterial infection of humans having depressed immunity, and retardation of the increase of tolerant bacteria caused by wide use of antimicrobials.

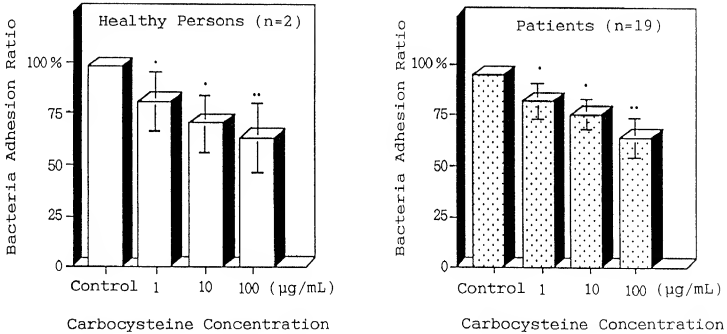


FIG.1

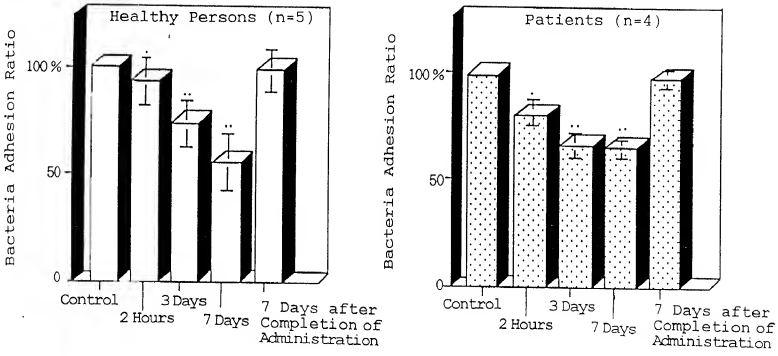


FIG. 2

DECLARATION FOR PATENT APPLICATION

As a below named inventor(s), I (we) hereby declare that:

My (our) residence(s), post office address(es) and citizenship(s) is (are) the same as stated below next to my (our) name(s).

I (we) believe I am (we are) an original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PREVENTIVE AGAINST RESPIRATORY INFECTIOUS DISEASES

the specification of which is attached hereto unless the following box is checked:

[x] was filed on December 22, 1998 as United States Application Number or
PCT International Application Number PCT/JP98/05810
and was amended on _____ (if applicable).

I (we) hereby state that I (we) have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I (we) acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I (we) hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):				
(Number)	(Country)	(Day/Month/Year)	Priority YES	Claimed: NO

I (we) hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(Application Number) (Filing Date)

I (we) hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I (we) acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulation, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing date)	(STATUS-patented, pending, abandoned)

DECLARATION FOR PATENT APPLICATION

I (we) hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and to act in accordance with the instructions from _____: HIKARI PATENT OFFICE.

Lloyd McAulay,	Reg. No. 20,423;	J. Harold Nissen,	Reg. No. 17,283;
Jules E. Goldberg,	Reg. No. 24,408;	Gerald H. Kiel,	Reg. No. 25,116;
Eugene LeDonne,	Reg. No. 35,930;	Samir R. Patel	Reg. No. 44,998
Daniel P. Lent	Reg No. 44,867		

all of McAulay Nissen Goldberg Kiel & Hand, LLP, 261 Madison Avenue, New York, New York 10016-2391.

Address all telephone calls to: Jules E. Goldberg, Esq. at Telephone No. (212) 986-4090

Address all correspondence to: Jules E. Goldberg, Esq.
REED SMITH, LLP
375 Park Avenue, 17th Floor
New York, New York 10152

I (we) hereby declare that all statements made herein of my (our) own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or 1st inventor (given name, family name):		Tsuyoshi Nagatake	
Residence:	Nagasaki, Japan	Citizenship:	Japanese JPX
Post Office Address:	c/o Institute of Tropical Medicine, Nagasaki University 12-4, Sakamoto 1-chome, Nagasaki-shi, Nagasaki 852-8523 JAPAN		
Inventor's signature: Tsuyoshi Nagatake		Date: 6 June, 2001	

Full name of sole or 2nd inventor (given name, family name):			
Residence:		Citizenship:	
Post Office Address:			
Inventor's signature: _____		Date: _____	

Full name of sole or 3rd inventor (given name, family name):			
Residence:		Citizenship:	
Post Office Address:			
Inventor's signature: _____		Date: _____	